
Numerical Calculation of Molecular Surface Area. I. Assessment of Errors

ANDREY A. BLIZNYUK* and JILL E. GREADY†

Department of Biochemistry, University of Sydney, Sydney, NSW 2006, Australia

Received 23 January 1995; accepted 3 August 1995

ABSTRACT

Several points distributions have been used to calculate van der Waals surface areas of a set of molecules. It is shown that there is no strict correlation between the global statistical characteristics of the points distribution, such as deviation and standard deviation, and the accuracy of the calculation of molecular surface. Information about details of the points distribution is needed for predicting the precision of the results. The results show that points distributions produced by optimization of the U function of Le Grand and Merz [*J. Comput. Chem.*, **14**, 349 (1993)] give the most accurate estimation of the molecular surface in numerical calculations. The precision of the numerical evaluation of the van der Waals surface areas has been assessed for 256, 512, 1024, and 2048 points on a single sphere. © 1996 by John Wiley & Sons, Inc.

Introduction

Because chemical processes occur in solution, solvent may have a significant influence on these processes, especially for biochemical systems. Calculation of the solvation energy is essential in theoretical investigation of processes such as protein folding, protein–ligand interaction, etc.¹ Because inclusion of explicit water molecules greatly increases the computational time, simpli-

fied models using molecular surface area or volume calculation as a measure of total solvation energy² or its hydrophobic component³ have been developed. There are now many algorithms reported in the literature for calculating the area of the van der Waals surface, Molecular Surface, and solvent accessible surface (refs. 4–6 and references therein). We will follow the nomenclature suggested in ref. 6 and use Molecular Surface (capitalized) as a particular form of surface as defined by Richards⁷ and molecular surface (lowercase) as a general descriptor of the surface of a molecule. These approaches use a model of molecules as a collection of fused spheres, with each sphere representing an atom or group of atoms. All these algorithms can be divided into two broad classes: analytical and numerical algorithms. The analyti-

* On leave from Novosibirsk Institute of Bioorganic Chemistry, Novosibirsk 630090, Russia.

† Author to whom all correspondence should be addressed at Division of Biochemistry and Molecular Biology, John Curtin School of Medical Research, Australian National University, Canberra, ACT 0200, Australia.

cal approach provides an accurate description of molecular surface. There are two main methods to calculate the van der Waals surface area analytically: using the inclusion-exclusion principle^{8,9} or spheres-planes intersections.¹⁰ Both these methods become rapidly impractical with an increase in the number of spheres used to represent the molecule, because of proportionality to K^2 , where K is the number of sphere-sphere intersections. Such algorithms are also very sensitive to roundoff errors. Recently, some progress in overcoming these problems has been made,¹¹ but, unfortunately, the speed of the calculation is still a bottleneck. The only known exception is the MSEED program,¹² which used the inclusion-exclusion principle truncated to the third order sphere-sphere intersections. Other simplifications used in this method allow for calculation of the solvent accessible area of large molecules, but this will be inaccurate for molecules with cavities and for calculation of van der Waals surface area.¹²

The numerical algorithms are useful because they give not only the value of the area, but also the positions of surface elements, which can be used in construction of boundary elements for different versions of reaction field theory (refs. 13 and 14, and references therein). The number of operations in numerical algorithms is, in general, proportional to $K * N$, where N is the number of points (or other elements) used to represent the surface of each sphere. There are a number of different implementations of this method,^{5,15-20} but only very limited data are available on the accuracy of the different versions. For example, 200 orientations of a single molecule have been used for estimation of the accuracy of an algorithm in ref. 5, while data for only three molecules are listed in ref. 20.

In this article we investigate the influence of points distribution on the accuracy of numerical surface area calculation.

Method

The numerical approach to the calculation of molecular surface area assumes that each molecule can be represented as a collection of fused spheres of different radii, with each sphere representing an atom or group of atoms. Each sphere is characterized by a collection of points on its surface. The coordinates of these points are usually obtained by projection of coordinates of points on the unit sphere to a sphere with radius R , that is, each

sphere (atom) has the same number of points. The algorithm systematically removes points lying inside of at least one sphere. It is obvious that the precision of the surface area calculation will be determined by the number of points and their distribution on the sphere surface. It is also obvious that the more equally points are distributed on the surface, then the greater the precision of the computation will be. Unfortunately, the optimal distribution of the N points on a sphere surface is unknown for $N > 24$,²¹ and this is one of the reasons for the introduction of several different approaches. For example, the simple cubic grid has been used in ref. 16, two different versions of the slicing scheme are described in refs. 18 and 19, and the gnomonic projection of tessellation of the pentakis dodecahedron was introduced in ref. 17. Recently, the nongnomonic tessellation of the icosahedron and the pentakis dodecahedron has been described.²⁰ The most rigorous approach has been used in ref. 5. Here, the configuration of the N surface points has been determined by minimizing the potential $U(1)$. The minimum of this function occurs when points are maximally dispersed on the surface of the unit sphere²:

$$U = \sum_{i < j} (\pi - \beta_{ij})^2 \quad (1)$$

where β_{ij} is the arc length in radians between points i and j .

We choose to compare the points distributions obtained from the slicing scheme,¹⁸ from the gnomonic²² and nongnomonic²⁰ tessellations of the icosahedron and the pentakis dodecahedron, from the minimization of the U function (1), and from the minimization of a Q potential (2), which is the energy of repulsion of unit charges on the sphere surface,

$$Q = \sum_{i < j} 1/r_{ij}, \quad (2)$$

where r_{ij} is the distance between points i and j . It should be noted that there are several different variants of tessellation of Plato's bodies. For a good review and definition of nomenclature, see the recent article by Spackman.²² Here, we restrict ourselves to type $\{3,5+\}_{h,0}$ tessellation.²² Only that type of tessellation is implemented in the program NSC.²⁰ Also, our preliminary investigations showed that the properties of the points distributions from other tessellation types are not much different from those for the $\{3,5+\}_{h,0}$ tessellation. The tessellations of the gen-

eral type $\{3, 5 + \}_{h,k}$ generate spherical triangles covering the surface of the unit sphere. This allows us to select the centers of the spherical triangles¹⁷ or the vertices²⁰ as the actual points distribution. We used both these approaches. The selection of the centers of the spherical triangles is denoted x to avoid confusion.

The gnomonic tessellations of the icosahedron and pentakis dodecahedron have been obtained using the program of Spackman.²² The non-gnomonic tessellations of the icosahedron and pentakis dodecahedron have been generated using the program NSC.²⁰ The data for the slicing scheme¹⁸ have been generated using a modified version of the AMSOL program.²³ The U and Q points distribution have been obtained using 100 BFGS²⁴ optimization runs from randomly selected starting configurations. The lowest values obtained are $U(256) = 94944.659$, $Q(256) = 30506.930$, $U(512) = 382200.812$, $Q(512) = 124674.415$, $U(1024) = 1533708.925$, and $U(2048) = 6144733.727$. Due to computer time limitations, results for only U function optimizations have been obtained for 1024 and 2048 points and only 48 optimizations have been done for 2048 points. We should not expect much difference between U and Q functions for a large number of points (N) on the unit sphere, because in the limit of infinite N these two functions coincide.

We used Voronoi spherical polygons²⁵ constructed around each point to estimate the quality of the points distribution on the surface of the unit sphere. These polygons have been built using a modified algorithm of ref. 26. A similar approach was used for the same purposes in ref. 20. For the ideal points distribution, the surface of each Voronoi polygon should be equal to $4\pi/N$, where N is the number of points on the surface of the unit sphere. The relative values of the average deviation (3), standard deviation (4), and maximum deviation (5) from this value are listed in Table I for all points distributions used in this article:

$$D = (100\%/N) \sum_{i=1}^N |S_i/(4\pi/N) - 1| \quad (3)$$

$$SD = 100\% \left[\left(1/(N-1) \right) \sum_{i=1}^N (S_i/(4\pi/N) - 1)^2 \right] \quad (4)$$

$$\max D = 100\% * \max_{i=1, \dots, N} (|S_i/(4\pi/N) - 1|), \quad (5)$$

In eqs. (3)–(5), S_i is the surface area of point i . We used relative deviations (in percent) to allow comparison between points distribution with different N . In Table I points are grouped together for approximately 250, 500, 1000, and 2000 points.

Two approaches have been proposed for the evaluation of molecular surface area, after selection of accessible points. The simplest way is to assume that all points contribute equally to the surface area and then calculate the surface using eq. (6)^{5, 15, 16, 18, 19}:

$$A = \sum_i 4\pi R_i^2 M_i / N, \quad (6)$$

where M_i is the number of accessible points on sphere i and the summation is over all spheres (atoms) in the molecule. Such an assumption is not exactly valid even for the best points distribution we have (see Table I). A more accurate approach [eq. (7)] has been used in ref. 17:

$$A = \sum_i R_i^2 \sum_j^{M_i} S_j, \quad (7)$$

where S_j is the area (in radians) corresponding to each point. Only values obtained using eq. (7) are listed in Table I. Our calculations show that in most cases utilization of formula (6) gives close results: the difference in relative deviations is usually less than 0.01%. Only for poorly balanced points distributions, that is, tessellations of the icosahedron or the slicing scheme,¹⁸ might the difference be significant. For example, for tessellation 10 of the icosahedron [t i(10) in Table I], the deviation became 0.427% [0.309% by eq. (7)], and for tessellation 14 of the icosahedron [t i(14) in Table I], the deviation became 0.332% [0.163% by eq. (7)]. The use of eq. (6) for 256 points obtained from the slicing scheme¹⁸ gives the average deviation of 1.012% [0.627% by eq. (7)], and for 522 points the deviation became 0.875% [0.560% by eq. (7)].

For evaluation of the precision of the surface area calculations, a set of 197 molecules as listed in ref. 18 (all compounds except for monatomic) has been selected. This set is judged large enough to allow estimation of accuracy with reasonable confidence. The geometrical parameters of the molecules have been optimized by the AM1 method²⁷ using a modified version of the program

TABLE I.
Results for the Quality of the Different Points Distributions and Precision of the van der Waals Surface Area Calculations for the Set of 197 Molecules.

Method ^b	<i>N</i> ^c	Points Distribution ^a			Surface Area Calculations ^a		
		<i>D</i> ^d	SD ^e	max <i>D</i> ^f	<i>R</i> ^g	max <i>R</i> ^h	Norm <i>R</i> ⁱ
t d(2) x ^j	240	0.87	0.88	0.96	0.800	2.58	0.750
tn d(2) x ^j	240	0.87	0.88	0.96	0.800	2.58	0.750
t i(5)	252	8.67	10.79	28.41	1.066	7.51	1.049
tn i(5)	252	2.21	3.13	10.94	0.544	2.60	0.536
q	256	1.04	1.92	7.77	0.517	1.73	0.517
u	256	0.76	1.45	6.28	0.489	1.44	0.489
sl	256	3.61	7.01	36.13	0.627	3.87	0.627
t d(3)	272	1.67	2.43	6.73	0.570	2.55	0.606
tn d(3)	272	1.11	1.81	7.28	0.550	2.20	0.584
t d(4)	482	2.96	3.60	12.46	0.417	2.11	0.392
tn d(4)	482	0.93	1.47	7.48	0.429	2.26	0.404
t i(7)	492	9.88	11.89	32.50	0.525	3.84	0.504
tn i(7)	492	2.00	2.69	11.17	0.430	1.97	0.413
t i(5) x	500	8.46	10.20	20.25	0.495	1.93	0.483
tn i(5) x	500	2.33	2.85	5.19	0.387	1.29	0.378
q	512	0.90	1.79	8.35	0.319	1.11	0.319
u	512	0.74	1.57	7.19	0.358	1.59	0.358
sl	522	2.64	5.56	41.34	0.560	3.49	0.571
t d(3) x	540	1.94	2.32	4.21	0.368	1.59	0.388
tn d(3) x	540	0.95	1.17	2.57	0.342	1.47	0.361
t d(4) x	960	2.68	3.19	6.81	0.246	1.39	0.231
tn d(4) x	960	0.86	1.11	2.82	0.242	1.44	0.226
t i(7) x	980	9.26	11.57	26.08	0.329	1.45	0.315
tn i(7) x	980	2.02	2.60	5.75	0.218	0.96	0.209
t i(10)	1002	10.18	12.57	35.51	0.309	1.88	0.302
tn i(10)	1002	1.86	2.41	11.29	0.186	0.63	0.182
sl	1017	1.06	3.12	31.10	0.271	1.44	0.269
u	1024	0.70	1.64	8.27	0.140	0.65	0.140
t d(6)	1082	3.29	4.15	12.46	0.189	0.77	0.200
tn d(6)	1082	0.77	1.15	7.62	0.194	0.97	0.205
t d(8)	1922	3.48	4.38	16.11	0.151	0.47	0.142
tn d(8)	1922	0.70	1.01	7.67	0.151	0.54	0.142
t i(14)	1962	10.38	12.86	32.04	0.170	0.98	0.163
tn i(14)	1962	1.77	2.26	11.35	0.116	0.40	0.111
t i(10) x	2000	9.97	12.41	30.45	0.198	0.96	0.193
tn i(10) x	2000	1.84	2.39	6.54	0.120	0.48	0.117
u	2048	0.62	1.10	7.90	0.101	0.39	0.101
sl	2069	0.53	2.20	32.66	0.154	0.71	0.156
t d(6) x	2160	3.15	3.96	9.93	0.117	0.54	0.123
tn d(6) x	2160	0.74	0.99	3.41	0.123	0.65	0.130

^aAll data are in percent.

^bt, gnomonic tessellation; tn, nongnomonic tessellation; d(h), tessellation of pentakis dodecahedron; h, level of tessellation (i.e., {3, 5 + }_{n,0}); i(h), tessellation of icosahedron; h, level of tessellation; sl, slicing scheme (ref. 18); u, points obtained by optimization of U function (1); q, points obtained by optimization of Q function (2); x, denotes selection of the centers of spherical triangles.

^cNumber of points on the surface of the unit sphere.

^dCalculated by eq. (3).

^eCalculated by eq. (4).

^fCalculated by eq. (5).

^gCalculated by eq. (8).

^hCalculated by eq. (9).

ⁱNorm *R* = *R***N* / *N*std, where *N*std equals to 256, 512, 1024, and 2048 for *N* close to 250, 500, 1000, and 2000, respectively.

^jGnomonic and nongnomonic tessellation of level 2 are equivalent; see ref. 20 for details.

MNDO-85 described in ref. 28. Van der Waals radii from Bondi²⁹ have been used in the calculations. The exact analytical van der Waals surfaces have been calculated using the program of Dodd and Theodorou.¹⁰ For each points distribution the relative deviation (8) and maximum relative deviation (9) have been evaluated and listed in Table I:

$$R = (100\%/N_0) \sum_i^{N_0} R_i$$

$$\text{where } R_i = \frac{|A_i(\text{calculated}) - A_i(\text{exact})|}{A_i(\text{exact})} \quad (8)$$

$$\max R = 100\% * \text{Max}(R_i), \quad i = 1, \dots, N_0 \quad (9)$$

N_0 in the above formulae is the number of molecules in the set (197). For comparison of the precision of molecular surface area calculations with slightly different numbers of points, the relative deviations have been normalized to a single value by multiplying the results by N/N_{std} . The values of N_{std} have been chosen equal to 256, 512, 1024, and 2048 for N close to 250, 500, 1000, and 2000, respectively. These normalized values are listed in the last column of Table I.

Results and Discussions

According to the data obtained (Table I), there is no exact correlation between the precision of the surface area calculation R and the quality of the points distribution D . Indeed, comparison of the data for the nongnomonic and gnomonic tessellation of the pentakis dodecahedron shows that while the qualities of the points distribution are drastically different, the relative deviations in the surface area calculations are practically the same. On the other hand, using nongnomonic tessellation of the icosahedron gives systematically better results than gnomonic tessellation for both points distribution and surface area calculations. According to the precision of the surface area calculations, the schemes for obtaining points distributions can be divided into three classes (see Fig. 1). The first class contains the slicing scheme of ref. 18 and gnomonic tessellation of the icosahedron, which gives the worst results. Both methods of selection of points on a surface in the tessellation (vertices and centers of triangles) give similar results. The second class consists of nongnomonic tessellation of the icosahedron and gnomonic/nongnomonic tessellations of the pentakis dodecahedron. The

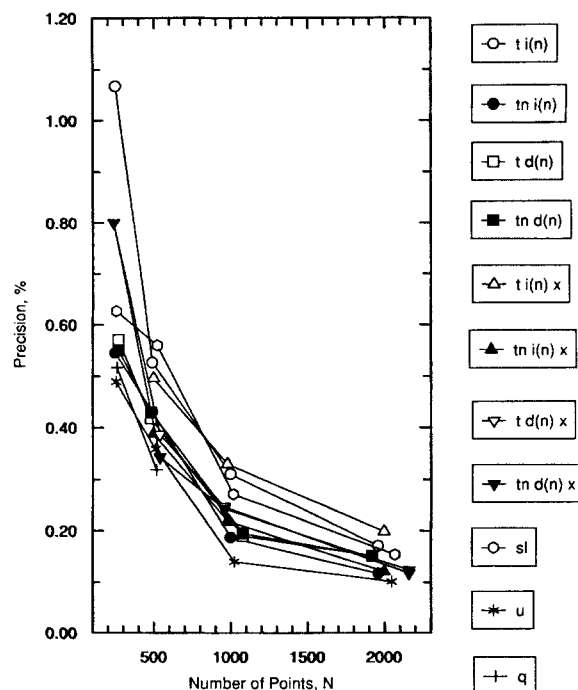


FIGURE 1. Dependence of precision (R) of the surface area calculations on the number of points for different points distributions. See footnotes for Table I for descriptions of the methods for obtaining the points distributions.

last class comprises points distributions obtained from optimization of the U and Q functions, which gives the best results.

From general considerations we can expect that doubling the number of points should reduce the value of the relative deviation R by half. Unfortunately, as our calculations show, the relative deviation reduces more slowly. To better illustrate this tendency we have plotted the normalized expected and obtained values of R for the tessellation of pentakis dodecahedron and U optimization in Figure 2. The forms of these curves are different. The deviation of the calculated values from the extrapolated ones for tessellation of the pentakis dodecahedron increases as N increases. Other tessellations (nongnomonic, tessellation of icosahedron) show similar behavior. The deviation from the expected values for U optimized points is irregular. This irregularity is not unexpected and reflects the difficulty of finding the global (or near global) minimum for a function with many minima. The systematic increase of the deviations for the tessellation schemes, in our opinion, is connected with a gradual compounding of the initial nonideality of the points distribution. The ideal points distribu-

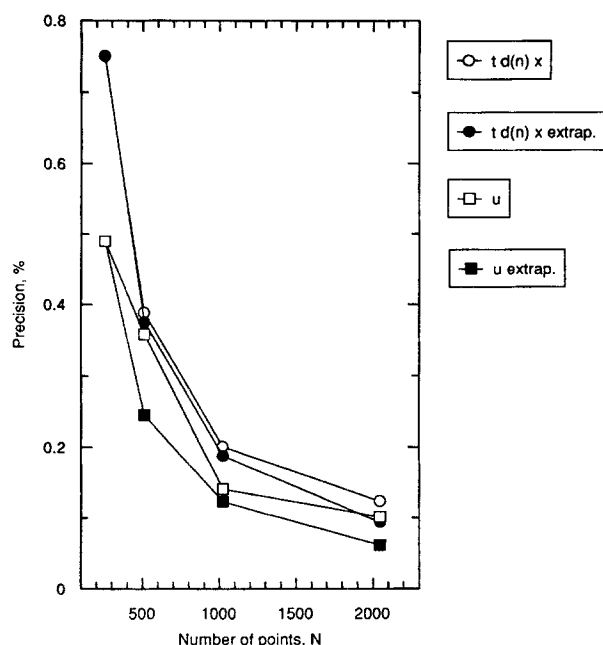


FIGURE 2. Comparison of extrapolated (solid symbols) and calculated (open symbols) behavior of the precision for the surface area evaluation for the tessellation of the pentakis dodecahedron (circles) and U optimization (squares) methods.

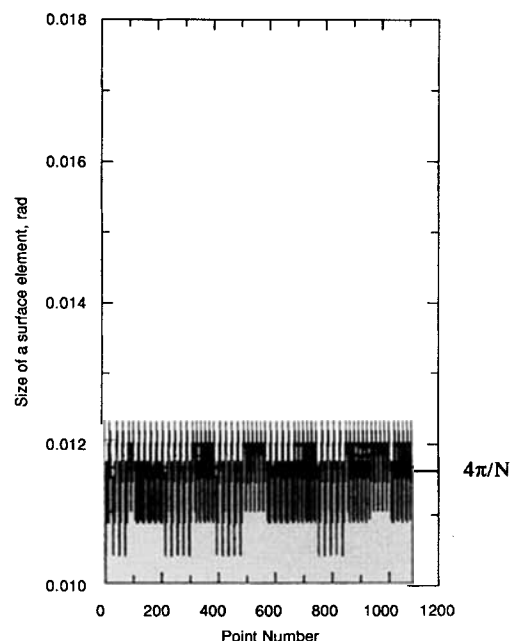


FIGURE 3. Size of the surface elements as obtained by building Voronoi spherical polygons around points from nongnomonic tessellation of the pentakis dodecahedron [tn d(6), 1082 points].

tions on the sphere surface corresponds to Plato's bodies.²¹ Making the tessellation introduces non-ideality into the points positions, i.e., points no longer have equal surface area. This nonideality increases as the level of the tessellation increases, because each tessellation $\{3, 5 +\}_{2h,0}$ contains points from the tessellation $\{3, 5 +\}_{h,0}$ plus some extra resultant nonideality. Obviously, the points distribution obtained as a result of the optimization of the $U(1)$ function does not have this systematic error.

Variations of the surface element sizes for the different points distributions are shown in Figures 3–5 for nongnomonic tessellation of the pentakis dodecahedron [tn d(6), 1082 points], U optimization (1024 points), and slicing scheme¹⁸ (1017 points), respectively. As can be seen clearly in Figure 3, tessellation produces a large number of small deviations from the ideal value $4\pi/N$ and only few relatively large deviations. This leads to small values of deviation D , standard deviation SD, and maximum deviation max D (Table I), which are commonly used as an index of distribution quality. The U optimization gives a large number of almost exact surface areas ($4\pi/N$), and also a number of relatively large deviations from this value (Fig. 4). The reflection of this is a small

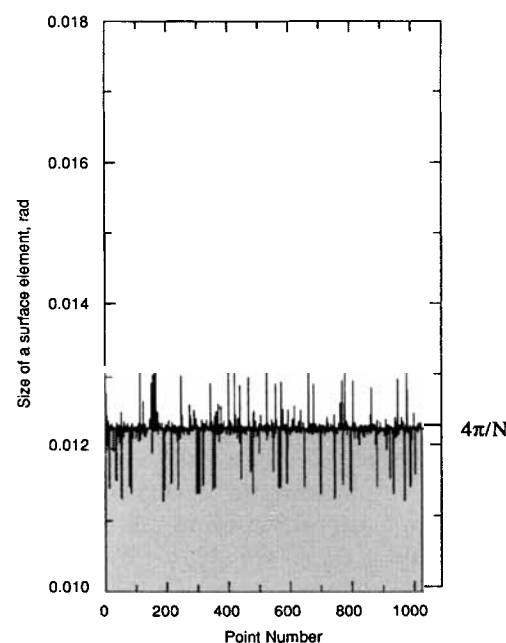


FIGURE 4. Size of the surface elements as obtained by building Voronoi spherical polygons around points from U optimization (1024 points).

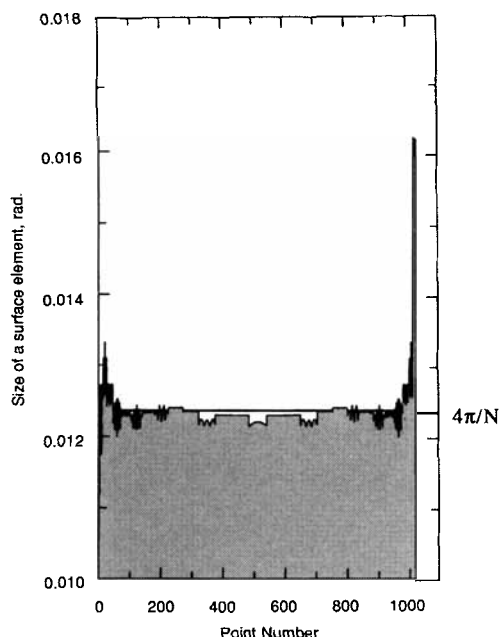


FIGURE 5. Size of the surface elements as obtained by building Voronoi spherical polygons around points from the slicing scheme (ref. 18; 1017 points).

value for the deviation D , but relatively large values of SD and $\max D$ (Table I). The slicing scheme¹⁸ (Fig. 5) gives very accurate values of surface area elements over most parts of the sphere. Unfortunately, very large deviations are concentrated near the poles. A similar pattern has been reported in ref. 20 for the slicing scheme described in ref. 19. This leads to very large $\max D$ values and relatively poor accuracy of the surface area calculations (Table I). Comparison of the precision of the surface area calculations (last column of Table I) clearly shows that the kind of distribution obtained from U optimization is best suited for the surface area calculations.

According to the results obtained, the best average accuracy for the molecular surface area calculations [for points distributions from $U(1)$ and $Q(2)$ optimization] is about 0.5%, with maximum deviation around 1.5%, for 250 points. For 500 points these values are approximately 0.3 and 1%, respectively. Increasing the number of points to 1000 will give an average accuracy around 0.15% and maximum deviation of 0.7%. Finally, for 2000 points we can expect an average precision of 0.1%, with maximum deviation around 0.4%. Is it possible to obtain better precision using the same number of points? According to extrapolated values for U optimization (Fig. 2), we can expect average deviations of approximately 0.25% for 500 points 0.13%

for 1000 points, and 0.065% for 2000 points. More effort (and luck) with optimization of the U function (1) is needed to get close to these values. If higher accuracy is required, then modifications to the numerical methods will need to be considered. For example, different numbers of points can be placed on different atoms depending on their environment and size. However, this will probably lead to an increase in the time for the computations. Realistically, if higher accuracy is needed, then it would be better to consider an appropriate analytical method.

Conclusion

Four different approaches for obtaining points distributions for molecular surface area calculations [slicing scheme,¹⁸ optimization of the U function (1), gnomonic and nongnomonic tessellation of the icosahedron and pentakis dodecahedron] have been studied. The results indicate that use of the points distribution obtained from optimization of the U function (1) gives the most accurate estimation of the molecular surface in numerical calculations. The reasons for poorer performance of the other approaches have been analyzed.

The following practical recommendations for the choice of points distributions can be made based on these data. If the required precision for estimation of molecular surface area lies within 0.5% ($\max R$ in Table I), the use of the U optimized points distribution is recommended. The coordinates of points for 256, 512, 1024, and 2048 points can be obtained from the authors. The use of the gnomonic or nongnomonic tessellation of the pentakis dodecahedron can be considered as a low CPU cost alternative. Due to the high computational cost for optimization of the U function for $N > 1000$, the tessellation of the pentakis dodecahedron seems the suitable choice if better than 0.5% precision in the estimation of molecular surfaces is required. The use of formula (7) is preferred to the simple approach (6) to avoid possible inaccuracy. This is especially important for poorly balanced points distributions. The program for generation of Voronoi polygons around points on the unit sphere can be obtained from the authors.

Acknowledgments

The authors thank Dr. L. R. Dodd, Dr. M. Spackman, and Dr. F. Eisenhaber for making their pro-

grams available. Useful discussions with S. S. Pachkovsky, Zurich, Switzerland, are acknowledged. Financial support from the National Health and Medical Research Council (NH & MRC) is gratefully acknowledged.

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